

## Literature Review

## Adhesion Prevention in Operative Laparoscopy

## Pencegahan Perlekatan pada Laparoscopi Operatif

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## Abstract

**Objective:** To know the modalities used for prevention of adhesion formation in operative laparoscopy.

**Method:** Literature study.

**Results:** Methods of prevention of adhesion in laparoscopy include: modification of surgical technique, anti-inflammatory agents, peritoneal instillates and barrier adjuvants. Modification of surgical techniques such as adherence to basic principles of microsurgery, the use of electrothermal bipolar vessel sealer, liberal irrigation of the abdominal cavity and instillation of a large amount of Ringer's lactate at the completion of the procedure. This technique alone, even though seems effective, is insufficient. The anti-inflammatory agents used are the NSAIDs, corticosteroids, antihistamines, progestogens, GnRH agonists and calcium channel blocker. But none of them demonstrated to be significantly effective. Barrier adjuvants consist of: oxidized regenerated cellulose (ORC) and expanded polytetrafluoroethylene (ePTFE) and peritoneal instillates are the crystalloids, icodextrin, hyaluronic acid (HA), solution of HA, viscoelastic gel, hydrogel, and fibrin sealant. There is insufficient evidence data regarding the methods above for the prevention of adhesiogenesis in laparoscopy. But one study evaluating the use of viscoelastic gel did significantly reduce adnexal adhesion in laparoscopy.

**Conclusion:** Laparoscopy does not truly eliminate the adhesiogenesis problem. No single therapy is effective for prevention of adhesion formation. The multimodal methods shall be used to increase the successful rate in adhesion prevention.

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**Keywords:** laparoscopy, adhesion, microsurgery, anti-inflammatory, peritoneal instillates, barrier adjuvants

## Abstrak

**Tujuan:** Untuk mengetahui modalitas dalam mencegah pembentukan perlekatan pada laparoscopi operatif.

**Metode:** Studi literatur.

**Hasil:** Metode pencegahan perlekatan pada laparoscopi termasuk: modifikasi teknik bedah, anti-inflamasi, penggunaan cairan ke dalam rongga peritoneum dan barrier adjuvan. Modifikasi teknik bedah seperti aplikasi prinsip-prinsip dasar bedah mikro, penggunaan kauter elektro termal bipolar, irigasi dari rongga peritoneum dengan sejumlah besar ringer laktat pada tahap penyelesaian prosedur. Teknik ini saja, meskipun tampaknya efektif, tidak cukup. Anti-inflamasi yang digunakan adalah NSAID, kortikosteroid, antihistamin, progestogen, agonis GnRH dan penghambat saluran kalsium. Tapi tak satu pun dari mereka terbukti efektif secara signifikan. Barrier adjuvan terdiri dari oxidized regenerated cellulose (ORC) serta expanded polytetrafluoroethylene (ePTFE) sedangkan cairan untuk rongga peritoneum adalah kristaloid, icodextrin, asam hialuronat (HA), larutan HA, gel viskoelastik, hidrogel, dan silen fibrin. Namun data-data yang ada mengenai metode di atas tidak cukup membuktikan dapat mencegah perlekatan pascalaparoscopi. Tapi satu studi mengevaluasi penggunaan gel viskoelastik secara signifikan dapat mengurangi perlekatan pada adneksa di laparoscopi.

**Kesimpulan:** Laparoscopi tidak menghilangkan masalah terjadinya perlekatan pascaoperasi. Tidak ada terapi tunggal yang efektif untuk mencegah pembentukan perlekatan. Pendekatan secara multimodalitas harus digunakan untuk meningkatkan tingkat keberhasilan dalam pencegahan perlekatan.

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**Kata kunci:** laparoscopi, perlekatan, bedah mikro, anti-inflamasi, instilasi rongga peritoneum, barrier adjuvan

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## INTRODUCTION

Post-operative adhesion formation is still a major complication of open laparotomy surgery or operative laparoscopy and a contributing factor that cause infertility, small bowel obstruction, ectopic pregnancy, abdominal or pelvic pain and increasing difficulty when reoperation is performed.<sup>1</sup> Adhesion actually results as a natural consequence of surgical trauma and healing. Operative injury will cascade several reactions that trigger adhesion formation through inflammation process, reactive oxygen species (ROS) which results in formation of fibrinous exudate.<sup>2-4</sup> The use of laparoscopy is less adhesiogenic than laparotomy, this was demonstrated by Dwight Chen<sup>5</sup> when com-

pared laparoscopy vs laparotomy in the porcine model to evaluate the adhesion formation. The result were significantly higher adhesion formation was observed in the laparotomy group than in the laparoscopic group. But a study done by Binda<sup>4</sup> demonstrated the use of CO<sub>2</sub> gas for the pneumoperitoneum during laparoscopy was cofactor in adhesion formation itself. Based on these studies, whether the surgical procedures are, it is important to consider the prevention of adhesion. Nowadays, there are many methods that can be used, which are: modification of surgical technique, anti-inflammatory agents, peritoneal instillates, and surgical adhesion barriers. This article shows the review of methods mentioned above.

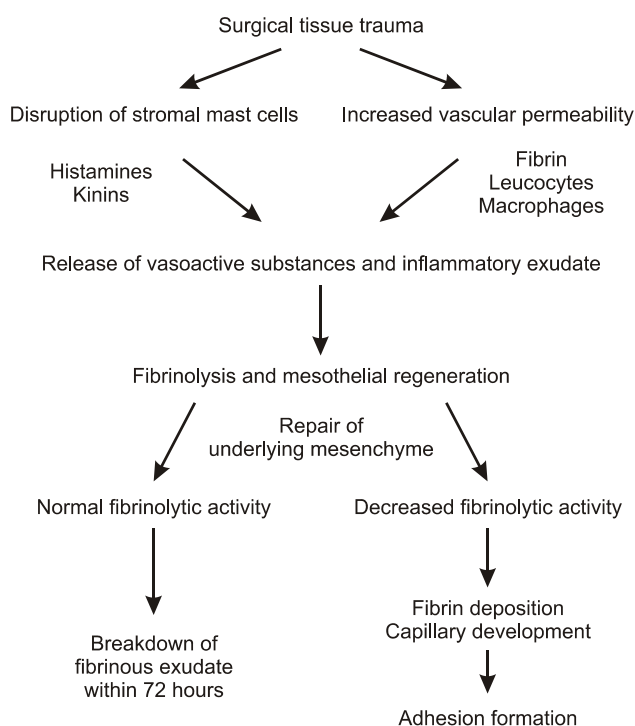
## PATHOGENESIS OF ADHESION

### Role of inflammation process

Surgical trauma or injury to the peritoneal tissue will triggers the breakdown of stromal mast cells and increased vascular permeability. Disruption of stromal cells will release histamine and kinin which will further increase the vascular permeability and induce the release of vasoactive substances and inflammatory exudates.<sup>1</sup> Increased of vascular permeability results in deposition of fibrin, leucocytes and macrophage which will release pro-inflammatory cytokines. In the physiologic process, fibrin-rich blood clot will be degraded by the fibrinolytic activity, which is Plasminogen-Activating activity (PAA) in the mesothelium, resulting in the repair of damaged tissue (mesothelial regeneration). In the presence of pro-inflammatory cytokines, the PAA is inhibited by the plasminogen activity inhibitor (PAI)-1 and 2 resulting in decreased fibrinolytic activity and formation of fibrous adhesion.<sup>1,2,6</sup> Summary of the process can be found on Figure 1.

Among the cytokines which take part in the adhesionogenesis, formation of blood vessels and the remodelling process are the transforming-growth-factors (TGF)- $\beta$  and the vascular endothelial growth factors (VEGF).<sup>6</sup>

### Postoperative adhesions.



ASRM Practice Committee. Peritoneal adhesions. Fertil Steril 2008.

**Figure 1.** Pathophysiology of adhesion formation.<sup>1</sup>

### Role of reactive oxygen species (ROS) and hyperoxia condition

Laparoscopy, eventhough claimed to be less adhesiogenic, is also a cofactor of adhesionogenesis. The use of CO<sub>2</sub> gas to make the pneumoperitoneum (insufflation/deflation process) has altered the mesothelial cells and peritoneal fluid that will result in ischaemia and reperfusion injury.<sup>4</sup> This injury will generate ROS and decrease ROS scavengers, such as catalases, superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). A study by Binda<sup>3</sup> using laparoscopy in mouse demonstrated that CO<sub>2</sub> gas will enhance the adhesion process. In the study, he developed three models in which different types of insufflation gas are used: the hypoxic model, in which pure CO<sub>2</sub> is used, corresponds to a traditional laparoscopy; the normoxia model, in which 3% oxygen is added to the pneumoperitoneum; and the hyperoxia model, in which 12% oxygen is added to the pneumoperitoneum, and which mimics open surgery because tissues are in contact with the high oxygen concentration of air. During these studies, he demonstrated that adhesion formation is increased using pure CO<sub>2</sub> pneumoperitoneum and when more than 10% oxygen is added to the pneumoperitoneum, in comparison with a CO<sub>2</sub> pneumoperitoneum with 3 - 4% of oxygen.

## PREVENTION OF ADHESION FORMATION

Methods of prevention of adhesion include: modification of surgical technique, minimizing tissue trauma, anti-inflammatory agents, peritoneal instillates and applying pharmacological and/or barrier adjuvants.

### Surgical technique

Laparoscopy is more superior than laparotomy because laparoscopy takes minimal access into the abdominal cavity by reducing peritoneal injury, avoiding incision through highly vascularized anatomical structures, reducing manipulation of structures distant from the operative site, and with its magnified view enables greater handling and more precise dissection of anatomical structures at the operative site, thus contributing to minimize the degree of tissue trauma.<sup>7</sup>

Besides that, the use of basic principles of microsurgery, liberal irrigation of the abdominal cavity and instillation of a large amount of Ringer's Lactate at the completion of the procedure will reduce the adhesionogenesis process.<sup>8</sup>

The use of developed instruments like electrothermal bipolar vessel sealer is associated with a reduced post-operative adhesion formation in comparison with ultrasonically activated scalpel and monopolar electrocautery. For surgical technique, in advanced endometriosis, temporary ovarian suspension is a technique for preventing periovarian post-operative adhesions. In case of laparoscopic myomectomy, subserous sutures are associated with significantly lower adhesion rate and higher pregnancy rate in comparison with interrupted 'figure 8' sutures.<sup>9</sup>

### Anti-inflammatory agents

The anti-inflammatory agents used for prevention of adhesion formation are the NSAIDs, corticosteroids, antihistamines, progestogens, GnRH agonists and calcium channel blocker. NSAIDs, corticosteroids and anti-histamines have shown to be effective in preventing adhesion formation in several animal studies, however there is no significant evidence from any published study to recommend their use in humans.<sup>1,7</sup> Progestogens have shown to be effective in preventing adhesion in laparotomy surgery but no data found in the setting of laparoscopy.<sup>7</sup> GnRH agonist works through inhibition of neoangiogenesis, improving fibrinolytic reactivity, and reduction of the degree of inflammation. Studies demonstrated that GnRH decrease adhesion formation in animal model. At present, no studies evaluate the use of GnRH in preventing adhesion formation in human laparoscopy.<sup>7</sup> Studies demonstrated that calcium-channel blocker is effective in reducing adhesion formation in animal models but never been followed with studies in human.<sup>7</sup>

### Peritoneal instillates and barrier adjuvant

Another methods for preventing the adhesion formation is using peritoneal instillates and barrier adjuvant. This scientific rationale behind the basic process is mechanical separation of peritoneal surfaces of the pelvic organs during the early days of the healing process. Barrier adjuvants consist of: oxidized regenerated cellulose (ORC) and expanded polytetrafluoroethylene (ePTFE). Peritoneal instillates consist of: crystalloids, icodextrin, hyaluronic acid (HA), solution of HA, viscoelastic gel, hydrogel, and fibrin sealant.<sup>7</sup>

Oxidized regenerated cellulose reduces adhesion formation by transforming into gelatinous mass covering the damaged peritoneum and forming a barrier physically separating adjacent raw peritoneal surfaces. The use of ORC is associated with reduced incidence of both de novo and reformed adhesions. It is essential that complete hemostasis is achieved before ORC is placed on the peritoneal surface, as the presence of intraperitoneal blood negates any beneficial effect.<sup>1,7</sup>

Expanded polytetrafluoroethylene is a nonabsorbable adhesion barrier produced in thin sheets. This barrier has also been shown to decrease the severity, extension and incidence of adhesion. But its limits are this barrier must be sewn in place and should be removed at subsequent surgery so it is not applicable in laparoscopy.<sup>1,7</sup>

Crystalloid is the most popular and economic agent used for adhesion prevention. Instillation of large volume of crystalloid into the peritoneal cavity causes the 'hydroflotation' effect. However, because of the rapid absorption rate of the peritoneum, the crystalloid fluid will likely to assimilate into the vascular system within 24 - 48 hour so it will not reduce the formation of adhesion.<sup>10</sup>

Icodextrin is an  $\alpha$ -1,4 glucose polymer of high molecular weight, which is rapidly metabolized to glucose by the  $\alpha$ -amylase in the systemic circulation, but is absorbed only slowly from the peritoneal cavity.

The 4% solution of icodextrin, having a longer peritoneal residence time ( $\geq 4$  days) than crystalloid solutions, has the potential to significantly reduce post-surgical adhesion formation by means of a prolonged hydroflotation. Preclinical studies of icodextrin in animal model demonstrated a reduction in de-novo adhesion formation. But currently, there is no sufficient evidence in prevention of adhesion formation laparoscopy.<sup>10</sup>

Hyaluronic acid is a naturally occurring glycosaminoglycan and a major component of the extracellular matrix, including connective tissue, skin, cartilage and vitreous and synovial fluids. This polymer is biocompatible, nonimmunogenic, non-toxic and naturally bioabsorbable. Intraperitoneal instillation coats serosal surface, minimizes serosal dessication and reduces adhesion formation. However, its use after tissue injury is ineffective.<sup>11,12</sup>

Solution of HA is a liquid composed of 0.4% sodium hyaluronate (hyaluronic acid) in phosphate buffered saline, is applied intraoperatively, prior to dissection, to protect peritoneal surfaces from indirect surgical trauma or post-operatively to separate surfaces after they are traumatized. In animal models, this solution reduced serosal damage, inflammation and post-surgical adhesions. In human, no studies evaluating the role of solution of HA in preventing adhesion following laparoscopic gynecological procedures are available in the literature.<sup>13</sup>

Viscoelastic gel is a gel composed of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride specifically formulated for laparoscopic application, with tissue adherence and persistence sufficient to prevent adhesion formation. Studies done by Lundorf et al<sup>14</sup> demonstrated that viscoelastic gel did significantly reduce adnexal adhesions in patients undergoing gynaecological laparoscopic surgery.

Hydrogel is two synthetic liquid precursors that, when mixed, rapidly cross-link to form a solid, flexible, absorbable hydrogel. The solid polymer acts as an adhesion barrier and it can be easily applied by laparoscopy. The currently available evidence does not support the use of hydrogel either in decreasing the extent of adhesion or in reducing the proportion of women with adhesions.<sup>7</sup>

Fibrin sealant is a two-component substance that can be applied as a liquid solution to the tissue. The mixture of the two substances becomes a highly polymerized solid fibrin film. Clinical data regarding the use of fibrin sealant in prevention of adhesions are limited.<sup>7</sup>

### CONCLUSION

Adhesion is still a major contributor for infertility, small bowel obstruction, ectopic gestation, abdominal or pelvic pain and difficulty when reoperation. Laparotomy is more likely to be adhesiogenic than laparoscopy. But, even though laparoscopy claimed to be less adhesiogenic, however it does not truly eliminate the problem. Therefore, many modalities have been developed to at least minimize this adverse event, which are: modification of surgical technique, anti-inflammatory agents, peritoneal instillates, and surgical adhesion barriers.

Many clinical reviews show that there is still no single therapy is proven highly effective for prevention of adhesion formation. Although some of it show promising result. Perhaps in the future, the multimodal or combined methods shall be used to increase the successful rate in adhesion prevention. Further research on this subject shall be conducted.

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